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Mini Review

Unraveling the Role of $NLRP_3$ Inflammasome in Gliomas: Implications for Tumor Progression and Therapeutic Strategies

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Abstract

The $NLRP_3$ inflammasome has emerged as a critical player in the pathogenesis of gliomas, influencing tumor growth, immune evasion, and the tumor microenvironment. This review explores the multifaceted role of $NLRP_3$ in glioma biology, highlighting its activation mechanisms and the subsequent release of pro-inflammatory cytokines, such as IL-1β and IL-18. We discuss the relations between these inflammatory mediators and tumor progression. In addition, we described the role of $NLRP_3$ inhibition in mediating the protective effect of various potential therapeutic interventions. Furthermore, we examine current therapeutic approaches targeting $NLRP_3$, including small molecule inhibitors and combination therapies, which hold promise for enhancing anti-tumor effect and improving patient outcomes. By integrating insights from recent research, this article underscores the potential of $NLRP_3$ as a therapeutic target in glioma treatment, paving the way for novel strategies to combat this challenging malignancy.

Keywords: Glioma; NLRP 3inflammasome; caspase 1; IL-18; IL-1β; cancer

Introduction

Glioma had emerged as the most prevalent primary tumor of the central nervous system (CNS) (~80%) affecting around 6 per 100,000 individuals within United States [1]. Patients suffering from glioma generally exhibit poor outcomes particularly owing to their highly aggressive proliferation and relapses [2]. Standard therapies typically include surgical resection, followed by radiation, chemotherapy (often with temozolomide). Despite these approaches, the benefits are still unoptimistic with only 5.5% of patients manage to survive after 5 years of diagnosis [3]. Therefore, investigating the mechanisms of glioma metastasis is vital for advancing our understanding of the disease and translating that knowledge into improved clinical strategies, ultimately benefiting patients with this aggressive brain tumor.

$NLRP_3$ Inflammasome

Glioma microenvironment is characterized by the chronic accumulation of inflammatory markers in order to activate microglial cells and promotes the infiltration of leukocytes that eventually amplify the inflammatory responses [4]. One such mediator is NOD-like receptor family pyrin domain-containing 3 ($NLRP_3$) inflammasome. $NLRP_3$ inflammasome is an oligomeric complex that consists of ($NLRP_3$), apoptosis-associated speck-like protein (ASC)

and procaspase-1. Upon receiving appropriate stimulus such as damage-associated molecular patterns (DAMPs), $NLRP_3$ mediates the activation and release of IL-1β and IL-18 [5,6]. The expression of $NLRP_3$ inflammasome is particularly confined to astrocytes and glial cells [7]. Activation of $NLRP_3$ inflammasome plays a pivotal role in neurodevelopment as 4-month-old mice deficient in $NLRP_3$ exhibits cognitive impairment and synaptic dysfunction [8]. However, uncontrolled activation of $NLRP_3$ activation contributes towards the pathogenesis of several neurological disorders including gliomas.

Role of $NLRP_3$ Inflammasome in Glioma

Tarassishin et al reported for the first time reported the secretion of IL-1β by glioma cell lines as well as patients derived glioma cells. In addition, they observed that treatment U251 and U87 cells with IL-1β resulted in the activation of Signal transducer and activator of transcription 3 (STAT3), a transcription factor responsible for the cancer progression including gliomas [9]. A clinical study reported that the expression level of $NLRP_3$ and caspase 1 increases with the severity of gliomas and higher expression is associated with lower survival rate [10]. Similar findings were made by Bihan et al, who reported that $NLRP_3$ activation plays a crucial role in the maintenance of inflammatory conditions in tumor microenvironment [11]. Furthermore, tumor tissue samples collected from the glioma patients displayed a higher expression of $NLRP_3$ when compared to normal tissue [12]. $NLRP_3$ activation contribute towards the glioma cells proliferation, invasion epithelial-mesenchymal transition via activation of nuclear factor kappa B (NFκB) and phosphatase and tensing homolog (PTEN)/AKT signaling pathways [13]. Several studies reported that inhibition of $NLRP_3$ plays a crucial role in mediating the protective effects of various compounds possessing therapeutic potential against gliomas including β-Hydroxybutyrate, alendronate, and simvastatin (Table 1). Moreover, resveratrol inhibits the cells viability in metastatic cells via Janus kinase 2 (JAK2)/STAT3 signaling dependent inhibition of $NLRP_3$ inflammasome [14].

$NLRP_3$ Inhibitors

Several synthetic compounds have been designed and developed that exhibit inhibitory activity against $NLRP_3$ inflammasome. In 2001, a library of diary sulfonylurea-containing compounds were screened for their ability to inhibit IL-1β processing [15] and among them MCC950 was identified as the most potent and selective inhibitor of $NLRP_3$ inflammasome with an IC50 value of7.5 nM [16]. Harrison et al developed novel ester-substitutes of MCC 950 and identified two compounds with a better inhibitory potential on IL-1β secretion in the whole blood [17]. AMS-17, a novel sulfonylurea-derived compound, inhibits $NLRP_3$ inflammasome and prevented caspase 1 activation in the microglial cells upon stimulation with LPS [18]. JC124 is a benzene sulfonamide analogue that can inhibit $NLRP_3$ with an IC50 value of 3.25 μM [19]. However, these molecules have not been evaluated for their therapeutic potential against gliomas and therefore, a requirement exists for future research in that direction.

Conclusion

In conclusion, the $NLRP_3$ inflammasome plays a pivotal role in the pathophysiology of gliomas, influencing both tumor progression and the surrounding immune environment. By driving chronic inflammation and modulating immune responses, $NLRP_3$ contributes to the malignancy and resilience of these tumors. Targeting this inflammasome presents a promising therapeutic strategy that could enhance treatment outcomes by re-establishing immune surveillance and mitigating pro-tumorigenic inflammation. As research continues to uncover the complexities of $NLRP_3$'s involvement in gliomas, the development of specific inhibitors and combination therapies may pave the way for more effective and tailored treatments, offering new hope for patients facing these challenging brain tumors (Table 1).'

Table 1: Role of $NLRP_3$ inhibition in the anti Tumor effect of different compounds.

Compound name	Chemical nature	Model used	Effects	Ref.
β-Hydroxybutyrate	Ketone body	C6 glioma cells	Migration	[20]
Alendronate	Bisphosphonates	U87-MG cells	Apoptosis Mitochondrial Damage	[21]
Simvastatin	Statins	U87 and U251 cells	Apoptosis Migration	[22]
IP-Se-06 (3-((2-methoxyphenyl)selanyl)-7-methyl-2-phenylimidazol[1,2-a]pyridine)	Selenylated imidazole	A172 cells	Apoptosis	[23]
miR-223-3p	miRNA	U251 and U87 cells	Apoptosis Migration	[24]
Temozolomide magnetic temperature-sensitive liposomes (TMZ/Fe-TSL)	Liposomes loaded with drug	U87 cells and U251 cells	Apoptosis Reactive oxygen species (ROS)	[25]
Reseveratrol	Polyphenol	LN-229 and U87-MG cells	Apoptosis Migration	[14]

Conflict of Interest

No conflict of Interest.

Acknowledgment

None.

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